CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020766

PHARMACOLOGY REVIEW(S)

Hess

MAR 1 1999

NDA 20-766

25 Feb 99

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

Submission: dtd. 21,22 Jan 1999

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Labeling

Xenical (Orlistat) Capsules, 120 mg

Antiobesity agent; lipase inhibitor (long acting)

Indications and Usage: XENICAL is indicated for long-term (up to 2 years) weight management including weight loss and weight maintenance when used in conjunction with a mildly hypocaloric diet. XENICAL is also indicated to reduce risk for weight regain after prior weight loss.

Dosage and Administration: The recommended dose of XENICAL is one 120 mg capsule three times daily with each main meal (during or up to 1 hour after the meal). If a meal is missed or contains no fat, the dose of XENICAL can be omitted.

Convey to the Sponsor: See next page re Labeling.

Labeling:
CLINICAL PHARMACOLOGY:
Pharmacokinetics: Absorption:

It would appear that the sentence "Studies in animals indicated that the absolute bioavailability of orlistat was <1%." refers to the amount of intact orlistat that reaches the systemic circulation. This section is under the purview of Biopharm. and has been discussed previously with Dr. Robert Shore regarding suitability of inclusion of this sentence in the clinical pharmacology section. This section will be handled by Biopharm.

Labeling Needs Revision:
Pregnancy: Teratogenic Effects: Pregnancy Category B.

The word "basis" should be added to the end of the last sentence of the second paragraph so that it reads as follows:

> This finding was not reproduced in two additional rat teratology studies or in the rabbit teratology study at doses up to 23 and 47 times, respectively, the daily human dose calculated on a body surface area (mg/m^2) basis.

The sponsor has changed the Pregnancy section to indicate that XENICAL is not recommended for use during pregnancy.

The Nursing Mothers section has been changed to indicate that XENICAL should not be taken by nursing women.

These changes made by the sponsor in the preclinical portion of the Precautions section of the labeling are acceptable.

Convey to the Sponsor:
Pregnancy section:

[redacted]
DRAFT LABELING

[redacted]
/S/

cc: Original NDA 20-766; HFD-510 NDA 20-766; HFD-870 RShore
HFD-510 RSteigerwalt; HFD-510 DHertig; HFD-510 MHess

David H. Hertig
Pharmacologist

Incorporate change into new label.

[redacted]
/S/

3/1/98

[redacted]
APPEARS THIS WAY ON ORIGINAL

JUN 17 1997

NDA 20-766

13 June 97

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

Submission: dtd. 3 Jun 97; Rec'd 4 Jun 97

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Labeling

Xenical (Orlistat, Tetrahydrolipstatin) capsules

Antiobesity agent; lipase inhibitor (long acting)

Indications and Usage: Xenical is indicated for long-term weight control (weight loss, weight maintenance and prevention of weight regain) when used in conjunction with a mildly hypocaloric diet.

Dosage and Administration: The recommended dose of XENICAL is one 120 mg capsule three times daily with each main meal (during or up to 1 hour after the meal). If a meal is missed or contains no fat, the dose of XENICAL may be omitted.

LABELING: Labeling needs revision.

The first paragraph of the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the labeling needs to be changed. The multiples of the human dose calculated on a body surface area (mg/m^2) are not correct. In addition the sentence with reference to safety factors, calculated based on plasma levels, should be deleted.

Thus, the paragraph,

DRAFT LABELING

should be changed to read as follows:

DRAFT LABELING

APPEARS THIS WAY ON ORIGINAL

In addition the following section needs to be modified:

CLINICAL PHARMACOLOGY:

Pharmacokinetics: Absorption:

DRAFT LABELING

[redacted]

This point has been discussed with Biopharm and we suggest that the sentence does not belong in the clinical section and should be deleted. However, this section of the labeling is under the purview of Biopharm and the final decision will have to be made by them. Should the decision be made to retain this finding in the labeling, the sentence should be reworded to prevent ambiguity.

APPEARS THIS WAY ON ORIGINAL

/S/ [redacted]

David H. Hertig
Pharmacologist

cc: Original NDA 20-766; HFD NDA 20-766; HFD-870 RShore
HFD-510 RSteigerwalt; HFD-510 DHertig; HFD-510 MHess

/S/ [redacted] 6/16/4

APPEARS THIS WAY ON ORIGINAL

NDA 20-766

Date 22 April 97

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

Submission: Original: dtd. 26 Nov 96; Rec'd. 27 Nov 96
SU: dtd 9 April 97; Rec'd. 11 Apr 97

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary and Submission dtd. 9 Apr 97

Xenical (Orlistat, Tetrahydrolipstatin) capsules

Antiobesity agent; lipase inhibitor (long acting)

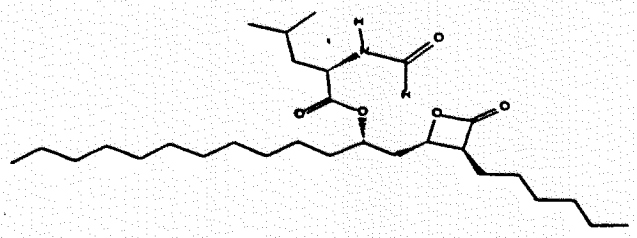
Indications and Usage: Xenical is indicated for long-term weight control (weight loss, weight maintenance and prevention of weight regain) when used in conjunction with a mildly hypocaloric diet.

Related: IND [redacted]

Dosage Form: 120 mg capsules

Dosage and Administration: The recommended dose of Xenical is one 120 mg capsule three times daily with each meal (during or up to 1 hour after the meal). If a meal is missed or contains no fat, the dose of Xenical may be omitted. The therapeutic benefits of Xenical (including weight control and improvement of risk factors) are continued with long-term administration. The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate and protein should be distributed over three main meals.

Chemical Structure: Ro 18-0647/008(polymorph B) designates a fine-milled white crystalline powder.



(S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-dodecyl(S)-2-formamido-4-methylvalerate (micropowd. 50 micro-m)

Regulatory Action: Pharmacology recommends approval.

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cc:Original NDA 20-766; IND [redacted] HFD-510 NDA 20-766;
IND 37,617; HFD-345; HFD 900 JContrera;
HFD-510 RSteigerwalt; HFD-510 MHess

/S/ [redacted]
David H. Hertig
Pharmacologist

/S/ [redacted]

4/28/97

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[redacted]

[redacted]

APPEARS THIS WAY ON ORIGINAL

All studies initiated after July 20, 1990, including a 1-year oral toxicity study in dogs maintained on a high fat diet and the oncogenicity studies were conducted with the fine milled polymorph B (Ro 18-0647/008), the physical form used in all pivotal clinical trials and the form intended for marketing. The available data suggested that the two polymorphic forms are pharmacacologically equivalent.

Several intravenous toxicity studies were conducted with liquid formulations of orlistat; these are designated Ro 18-0647/009, Ro 18-0647/024, and Ro 18-0647/053. In one study in rats, the test articles, designated Ro 18-0647/081, and Ro 18-0647/090, were pellets containing 50% active ingredient.

Phase 3 clinical trials used a pellet formulation while the dosage form used in the Phase 2 studies was a wet granulation formulation. Pharmacology requested comparison of the two formulations (IND[12]): although there are some differences in the composition of wet granulation and pellet formulation as well as in the dissolution media used, the dissolution profiles were identical for the 2 formulations, suggesting similar bioavailability.

Preclinical Studies:
Additional (more recent) Pharmacology, Toxicokinetic, ADME etc. Studies:

Single Dose-Response Study of Ro 18-0647/008 in Meal-Fed Rats. Effects on Activity of Gastrointestinal Lipases, Fat Absorption, and Gastric Emptying of Fat and Orlistat: F. Hoffmann-La Roche Ltd Research Report B-162'808 dtd. Nov 1996.

The effect of orlistat on gastric emptying and small intestinal transit was investigated. Female SPF Füllinsdorf rats were adapted to 4 days meal feeding of a 40 cal% fat diet (Kliba 343 25 g, casein 6.2 g, cellulose 12.5 g, tripalmitin 1.1 g, sucrose 0.75 g, olive oil 4.4 g, water 50 g) of one 10 g feeding in the morning and a second of 15 g at noon. On day 5, after fasting 16 hrs, rats were offered 10 g food containing 665 mg fat in the morning. After 20 min orlistat (0.15, 0.5, 1.5, 5, 15, 50 mg/kg) or vehicle (5% gum arabicum/5% milk powder, 5 ml/kg) was given orally. In another experiment, the drug was dissolved in the oil of the meal. Sacrifice was 1, or 4 hrs after start of the meal which usually lasted <1 hr.

Absorption is more potently inhibited when orlistat is dissolved in the fat of the meal (ID_{50} = 8 mole/kg) than when administered by gavage (ID_{50} = 21 µmol/kg).

It is reported that control rats showed qualitatively similar relative lipase activities in the stomach and in the different sections of the small intestine as in humans. Fat-admixed drug produced more marked suppression of lipolytic activity in the stomach, but the gavaged drug was more potent in the upper small intestine. However the inhibitory effect on overall lipolysis, was more marked with the fat-admixed drug as shown by the larger effect on either fat accumulation in the distal small intestine or on fecal fat excretion.

Significant lingual lipase was measurable in the stomach and high lipolytic activity was present in the lower small intestine.

The three major fat digesting enzymes, gastric, pancreatic and carboxylester lipase were inhibited by Ro 18-0647/008 in a dose-dependent manner and in all sections of the GI tract. Lipase activity following gavage was more potently inhibited than fat absorption. No appreciable effect on the rate of gastric emptying or small intestinal transit of dietary fat or radiolabeled drug was noted irrespective of the dose or fractional inhibition of fat absorption.

Effect of Orlistat After 8 Days Ingestion in Hamsters on Fecal Fat and Sterol Excretion and on Plasma Levels of Cholesterol and of Triglycerides: F. Hoffmann-La Roche Ltd Report B-164'748 dtd Aug 1996.

Male golden Syrian hamsters (Fume SPF from BRL) received 10 g/animal/day of a 40 cal% fat diet (Kliba Mühlen diet 2051) Each hamster ingested ca. 1.5 g fat/day and 0.5-0.6 mg cholesterol/day. Ro 18-0647/008 was mixed with the feed to give doses of 0, 50 and 0, 150 mg orlistat/kg b.w. (as two experiments) for 10 days for 2 animals/gp; controls 6/group per experiment.

Food intake and body weight development during drug intake remained within range of that of controls.

Fecal fat excretion for controls was about 4% of fat intake. This increased to 80 and 60% of fat intake at both doses of orlistat indicating inhibition of gastrointestinal lipases (number of animals too low for a dose relationship). Fecal cholesterol excretion was enhanced more than 8-fold above baseline, but coprostanol excretion only increased 1.5-2-fold. Both doses of orlistat reduced cholesterol absorption from a test meal containing radiolabeled cholesterol (controls above 90% absorption; orlistat less than 50% absorption). However, the absorption of radio labeled PEG marker was not influenced by orlistat administration.

Plasma cholesterol was reduced ca 50% with both doses of orlistat. Plasma triglycerides were reduced only with the high dose.

Orlistat: Antiobesity Properties and Effects on Lipid Metabolism in Genetically Obese (fa/fa) Rats: F. Hoffmann-La Roche Ltd Research Report B-103'374 dtd Nov 1996. Preliminary results.

Diet composition: chow diet 50%, casein 14%, tripalmitin 2%, olive oil 10%, sucrose 3%, cellulose 20%, 40% of calories as fat.

Obese (fa/fa) rats on 40 cal% diet were treated with 0, 4.7, 9.4, 42 mg/kg/day orlistat and TOE(?) 50% as fat for 11 weeks.

The effect on fat absorption was paralleled by body weight reduction which, in turn, was chiefly (79-98%) accounted for by loss of body fat. The intermediate dose totally reversed the obesity-inducing effect of the fat diet. The effect on fat absorption of the mid-dose group was matched by the TOE group dietary fat substitution. Weight gain and food intake were similar for both groups. Intestinal weights remained unaltered and no histopathological findings were observed. Bile acid excretion was not affected in any of the study groups.

Fat excretion was paralleled by reduced plasma vitamin E and reduced liver vitamins E and A. Prothrombin time (vitamin K dependent) remained unaltered. There were no alterations of plasma polyunsaturated fatty acids, and pancreatic weight and pancreatic lipase content were not affected.

Inhibitory Interaction of Orlistat with Gastrointestinal Lipases In Vitro. Potency, Reversibility and Partitioning of the Inhibitor Between Emulsified Triglyceride Droplets: F. Hoffmann-La Roche Ltd dtd Mar 1996.

In vitro studies in triglyceride emulsion assays showed orlistat to inhibit three GI lipases (gastric/lingual, pancreatic and carboxylester lipase) of rats, dogs and humans with a similar high potency.

Inhibition of pancreatic and carboxylester lipase was reversible in vitro (very slow) and associated with inactivation of orlistat.

Orlistat equilibrates and partitions very rapidly between triolein droplets in emulsions tailored to reflect conditions in the lumen of the duodenum.

Orlistat: Pharmacological Studies of Metabolites and Stereoisomers In Vitro: F. Hoffmann-La Roche Ltd Report B-162'805 dtd Oct 1996.

To determine the inhibitory potency of orlistat metabolites M1 (Ro 42-3988) and M3 (Ro 42-2556) the main metabolites present in human plasma, and by orlistat stereoisomers against pancreatic lipase and lipoprotein/hepatic lipase. M1 and M3 metabolites which are β-lactone ring opened (hydrolyzed) derivatives of orlistat were devoid of any inhibitory activity in assays of human pancreatic lipase at concentrations 4000x higher than the IC_{50} of orlistat. Only very weak inhibitory activity against rat and human lipoprotein/hepatic lipase was produced by M1 and M3. [Ester function of the β-lactone ring of orlistat is instrumental in the substrate-like inhibitory interaction with lipases.]

Marked differences were reported to have been noted in the lipase inhibitory potency in assays of porcine pancreatic lipase among stereoisomers of orlistat, but lesser differences were noted in assays of rat lipoprotein/hepatic lipase.

Studies of Orlistat in Diet-Induced Obese Rats: Roche Manuscript N-136302 dtd Oct 1996.

The purpose of this study was to determine whether intestinal hypertrophy is a characteristic finding in DIO (diet-induced obese) rats after long term treatment with orlistat. Moderately high fat diet of ca 15% fat, 53% carbohydrate (18% sucrose) and 16% protein produced obesity after 18 weeks. Mean daily orlistat over the 22 days of treatment was 10 and 28 mg/kg (7-8/gp). Controls gained 36 g, the low dose lost 9 g and the high dose lost 36 g. Even though rats continued to overeat (15-20%) for the remaining 10 days, cumulative intake was not significantly increased.

Orlistat caused a reproducible and dose-dependent increase in the wet weight of the small and large intestine. [No such effect was seen in genetically obese rats and mice.] These effects were not associated with detectable histological changes and were reversible following drug withdrawal. The increase in fecal dry weight appeared to closely parallel the effect on intestinal weight.

Dose-Response and Kinetics of Effects on Plasma Triglycerides after Single Oral and Intravenous Administration of Orlistat as a Micellular Dispersion in Mice and Rats: F. Hoffmann-La Roche Ltd Research Report B-162'810 dtd Nov 1996.

The purpose of this study in rats and mice was to characterize the kinetics of plasma triglyceride responses to oral orlistat, but particularly the reversibility kinetics following a hypertriglyceridemic effect.

Female RORO (Ibm) albino rats and female MORO (Ibm) albino mice were administered orlistat orally or intravenously as a dispersion in mixed micelle vehicle which contained 225 mM lecithin and 190 mM glycocholate. Dose levels of orlistat ranged between 0.3 and 100 mg/kg p.o. (2 ml/kg) and 0.03 and 10 mg/kg i.v. (1 ml/kg) in rats, and 1.5 and 150 mg/kg p.o. (2 ml/kg) and 0.01 and 10 mg/kg i.v. (1 ml/kg) in mice.

Following a single dose, plasma triglycerides increased very rapidly in a drug-related fashion, but the hypertriglyceridemic response was quickly reversed. However large the maximal response of plasma triglyceride concentration was,

there was hardly any biologically relevant residual change after 6 hours. According to the sponsor, it is possible that the rapid reversibility of hypertriglyceridemia is related to the high turnover of lipoprotein lipase at the vascular endothelium.

Evaluation of the Lipolytic Function of Hormone-Sensitive Lipase Following Single Intravenous Administration of Orlistat as a Micellar Dispersion in Rats: Research Report B-162'804. dtd. Oct 1996.

The purpose of this study was to determine whether at high systemic exposure achieved by i.v. injection of 10 mg/kg in rats, orlistat has any inhibitory effect on the lipolytic function of hormone-sensitive lipase which plays the rate-limiting role in the mobilization of fat stored in adipose tissue.

No appreciable inhibitory interaction with hormone sensitive lipase (located at the vascular endothelium or intracellularly) was evident. The lipolytic activity of Ro 40-2148, a β-adrenoreceptor agonist [which increases thermogenesis (energy expenditure) by stimulating fat mobilization and oxidation], as measured by the increase in plasma free fatty acid and free glycerol was not altered within the 6 hr observation period. This supports the notion that even at high plasma levels after intravenous injection, orlistat is not taken up to any relevant extent into the cytoplasmic cell compartment of adipocytes where the lipase is located.

Pharmacological Characterization of Ro 40-1379. Studies on In Vitro and In Vivo Interaction with Lipolytic Enzymes: Research Report B-162'811 dtd. Nov 1996.

Ro 40-1379 (M2) could formally be produced by initial hydrolysis of the N-formyl leucine ester linkage of orlistat. This putative metabolite is the only intermediate with intact β-lactone structure. Since the β-lactone ester structure is the key element responsible for lipase inhibition, Ro 40-1379 has the potential to act as a lipase inhibitor. However, Ro 40-1379 was not detected in plasma (detection limit ca 8 ng/ml), bile or urine in any of the species studied.

Ro 40-1379 is a very poor inhibitor of pancreatic lipase in vitro, but 4x more potent than orlistat as an inhibitor of rat lipoprotein/hepatic lipase. When incubated at room temperature with human plasma, the lipase-inhibiting activity was lost at least 10x more rapidly than that of orlistat. Following oral or i.v. administration in rats there was a substantially weaker effect on plasma triglycerides compared to orlistat. The threshold dose to induce a minimal effect on plasma triglycerides was considerably higher.

The sponsor indicates that, if formed at all (no appreciable levels were detected), Ro 40-1379 may be subject to faster biodegradation in vivo compared to the parent compound orlistat.

Two-Week Oral (dietary admixture) Toxicokinetic Study of Ro 18-0647/008 in Rats: [redacted] Project 359550; [redacted] 06452 dtd April 1996. Lot 3034010. Q.A. - Present.
[Metabolite Ro 42-3988 (M1): (2S,3S,5S)-5-[(N-formyl-L-leucyl)oxy]-2-hexyl-3-hydroxyhexadecanoic acid.]

A 2-week oral (dietary admixture) toxicokinetic study of Ro 18-0647/008 was carried out in rats [Wistar, Hanover-derived, outbred, SPF, 36/sex/gp (24/sex/gp

controls)] at doses of 150, 500 and 1000 mg/kg/day. Food consumption was increased (drug intakes compared favorably with nominal doses) without concomitant increase in rate of body weight gain. Plasma level data showed continuous exposure to unchanged Ro 18-0647 and to metabolite Ro 42-3988 [M1 metabolite [β-lactone ring opened (hydrolyzed) derivative of orlistat] throughout the 24 hour assessment interval. Ro 18-0647 plasma levels did not exceed 1000 ng/ml even though the daily dose was 1000 mg/kg which is consistent with poor absorption from the GI tract with high first-pass metabolism. Metabolite plasma levels were similar to that of Ro 18-0647. Plasma levels of parent drug and metabolite were more than dose-proportional which suggests metabolic saturation and/or increasing GI absorption with dose. Females had a systemic exposure to both drug and metabolite that was 1.3 to 1.6 fold greater than that of males. The kinetic parameters, maximum plasma concentration, minimum plasma concentration, and systemic exposure during a 24 hour interval (AUC_{0-24h}) for Ro 18-0647 and its metabolite Ro 42-3988 are as follows (from sponsor's tables):

	Nominal Dose 150 mg/kg/d	500 mg/kg/d	1000 mg/kg/d
C_{max} (ng/ml) Unchanged Ro 18-0647			
Male	15.5	144	595
Female	26.6	278	830
C_{max} (ng/ml) Metabolite Ro 42-3988			
Male	25.6	129	572
Female	48.3	248	563
C_{min} (ng/ml) Unchanged Ro 18-0647			
Male	1.89	45.5	151
Female	2.45	10.8	195
C_{min} (ng/ml) Metabolite Ro 42-3988			
Male	9.09	67.9	184
Female	18.1	33.9	241
AUC_{0-24hr} (ng•h/ml)Unchanged Ro 18-0647			
Male	230	2380	7690
Female	315	3150	12200
AUC_{0-24h} (ng•h/ml)Metabolite Ro 42-3988			
Male	387	2320	8600
Female	687	3010	9430

Two-Week Oral (dietary admixture) Toxicokinetic Studies of Ro 18-0647/008 in Mice: [redacted] Projects 324270 and 338051; [redacted] Studies 06112 and 06254, respectively). Research Report dtd. Nov 94. Lots 26031 and 26034 (2nd study). Q.A. - Present

Two 2-week oral (dietary admixture) studies of Ro 18-0647/008 were conducted in NMRI, SPF, Hanover-derived mice. Nominal doses were 0, 50, 500, 1000 and 2500 mg/kg/day in order to characterize pharmacokinetics and to support dose selection for a carcinogenicity study. There were 36/sex/group treated and 20/sex/control mice. After 14 days dosing, mice (3/sex/dose group/time interval) that were being dosed with Ro 18-0647/008 were bled from the retro-orbital plexus at two hour intervals for a total of 24 hours; following bleeding mice were sacrificed - no necropsies were performed or tissues retained. [The initial study [redacted] 324270) was repeated due to technical problems during assay and was not used for dose selection for the oncogenicity study.]

One 2500 mg/kg/day male died day 8 (causa morta undetermined). Food consumption was increased with no concomitant effect on body weight gain. Thus, drug intake was increased and doses ranged from ca 1.3 - 1.5-fold higher than nominal doses for both sexes.

Maximum mean Ro 18-0647 plasma exceeded 100 ng/ml for only three plasma samples in spite of ingestion of 3300 mg/kg/day by males and 3337 mg/kg/day for females. Plasma levels for the 50 and 500 mg/kg doses were below the limit of quantitation. The low systemic bioavailability (noted in other laboratory animals and humans)is attributed to low GI absorption and extensive first pass metabolism. Systemic exposure at the 1000 and 2500 levels was dose proportional for males and more than dose proportional for females. Systemic exposure at the 2500 mg/kg dose was similar for both males and females, the AUC_{0-24h} being 1077 ng•h/ml for males and 1028 ng•h/ml for females. However, for the 1000 mg/kg group, exposure was greater for males than females.

A 2.2 to 2.4 fold increase in actual daily dose resulted in a 2.2 and 3.7 fold increase in AUC_{0-24h} for males and females, respectively.

ex Sponsor's table:

Nominal Dose (mg/kg/d)	Actual Dose (mg/kg/d)	Male Mice Max. Mean Plasma Conc. (ng/ml)	AUC_{0-24h} (ng•h/ml)	Actual Dose (mg/kg/d)	Female Mice Max. Mean Plasma Conc. (ng/ml)	AUC_{0-24h} (ng•h/ml)
1000	1400	33.3	489	1485	25.8	281
2500	3330	98.6	1077	3337	73.2	1028

The actual doses, calculated from the food consumption data, were ca 1.4 times greater than the targeted doses. Therefore, the sponsor calculated the AUCs for the nominal doses of 1000 and 2500 mg/kg/day from the least-squares linear regression formulas:

	AUC (ng.h/ml) at Doses (mg/kg/day) of	
	1000	2500
Male Mouse	365	859
Female Mouse	181	724
M+F/2 (average)	273	792

Carcinogenicity Studies:

Oncogenicity (Feeding) Study with Ro 18-0647/008 - Polymorph B (Orlistat) in the Mouse: [redacted] Project 346860; Hoffmann-La Roche Study 06345 Research Report N-138886 dtd. Oct 1996. Study dates: May 93 - June 95. Lot No. 3034010 bulk drug [redacted] Q.A. - Present [Ro 18-0647/008 [redacted]]

Dose selection - A 13-week oral (dietary admix) toxicity study in mice did not provide sufficient information to aid in the selection of doses for the carcinogenicity study. Therefore, a 2-week oral (dietary admix) toxicokinetic study was conducted at nominal doses of 0, 50, 500, 1000, and 2500 mg/kg/day

orlistat. The sponsor calculated the AUC (ng.h/ml) for a nominal 1000 mg/kg dose as 365 for males and 181 for females (avg. M+F = 273) and for the 2500 mg/kg dose as 859 for males and 724 for females (avg. M+F = 792). An AUC of 13 ng.h/ml was given for the human therapeutic dose of 120 mg t.i.d. for a moderately obese (80 kg person). For the 1000 mg/kg mouse dose [Mouse:Human AUC ratio (273/13)] the multiple of the human dose was given as **21** times.

Pharmacology (HFD-510) felt that an exposure of 30 times the human therapeutic dose exposure would give a sufficient margin of safety. Since the sponsor's exposure calculations based on AUC indicated that a dose of 1000 mg/kg/day would give an exposure 21 times the human exposure on the therapeutic dose of 120 mg t.i.d., Pharmacology recommended a high dose of 1500 mg/kg in the mouse carcinogenicity study to give an exposure approximately **30 times** higher than the clinical situation.

The sponsor was informed that the mouse carcinogenicity study could be started with dose levels of 375, 750 and 1500 mg/kg/day.

Dose: 0, 0, 25, 375, 750, 1500 mg/kg/day (reported as 5897 mg/M^2/day) by dietary admixture (Groups 1-6)

Number of Animals: 50M;50F per dose (Allocation Group A)
Han IBM: NMRI mouse, SPF.
Additional mice (24/sex/group), assigned to Allocation Group B, were designated for interim sacrifice (6/sex/group) after 4, 26, 52, and 72 weeks.

Male mice were treated for 104 weeks and females for 95-96 weeks. Female groups were terminated early because of increased intercurrent mortality in all dose groups, including controls.

Diet: Kliba 30-343-7 (also known as Kliba 05-343-70) contains ca 22% of metabolizable energy as fat (79.4 mg/g) and 0.98% (w/w) of elemental calcium.

Vitamin Supplementation: Groups 4, 5, and 6 received vitamin supplementation weekly by gavage. Groups 1, 2, and 3 received vehicle (peanut oil) only. Groups 4, 5 and 6 - 0.1 ml/mouse: Vitamin A-alcohol - 1,260, 1,680, 3,360 µg/ml; D-alpha-Tocopherol - 80, 105, 210 mg/ml; Vitamin D_3 - 5, 7, 14 µg/ml; Vitamin K_1 - 1,000, 1,400, 2,800 µg/ml; Beta carotene - 1,000, 1,400, 2,800 µg/ml.

Results:

Allocation Group A - **Oncogenicity Animals**

Mortality: No treatment-related effects on survival were reported. Female groups were sacrificed after 96 weeks of dosing because all female dose groups, including the two control groups, were rapidly approaching 25% survival.

Clinical signs: No treatment-related clinical signs were reported.

Nodules and Masses: Compared to controls and within the same sex, the incidence, group distribution and localization of palpable masses were similar for all groups.

Bodyweight: Male (but not female) body weights of the high dose were slightly decreased (3-6%) during the first 41 weeks of study but not thereafter.

Food Consumption: Food consumption was increased in a dose-related manner in all treated male groups (14-31%) and in females (20-30%) at doses $\geq$ 375

mg/kg/day. Relative food consumption followed a similar trend. Average food consumption for the low dose females was increased ca 5% during treatment.

Drug Intake: The mean intake of Ro 18-0647/008 was 2-4% higher than that of the intended dose in males and females.

Hematology: Differential blood counts for females at 90 weeks and males at 101 weeks were within normal biological variation and comparable with controls.

Organ Weights: Male and female organ weight changes were not treatment-related. However, 750 mg/kg/day males showed increased testicular weight (absolute and brain weight ratio) and decreased pituitary to body weight ratio. Similar changes were not observed at 1500 mg/kg.

Necropsy - Gross Changes: Reported that there were no nodules, masses or any other gross anatomic changes noted at necropsy that were considered to be drug associated.

Histopathology: Changes were random or comparable with controls and affected mainly endocrine, reproductive and large parenchymatous organs. Findings were categorized mainly as acute/chronic inflammatory lesions or degenerative or hyperplastic changes. According to the sponsor, there were no apparent non-neoplastic treatment-related lesions. However, findings [control (2) thru high dose] included: Male heart - incidences of arterial thrombosis were 0, 2, 11, 5, 4, -; Male Adrenal cortices lipogenic pigment 14, 7, 25, 29, 21, 25; Male Adrenal Cortical Atrophy 1, 3, 7, 10, 10, 1; Male Mesenteric Lymph Node - Congestion 8, 5, 10, 12, 10, 11; Amyloidosis was increased over that of controls in several organs male and female. Joint/femur arthropathy and lymphoid hyperplasia of mandibular lymph nodes of female treated were greater than that of controls. Findings were in general considered by the sponsor to be similar in treated and controls.

According to the sponsor, treated and control findings were also similar for the number of primary neoplasms, the number of mice with primary neoplasms, the number of mice with more than one primary neoplasm, the number of mice with metastases, and the number of benign and malignant neoplasms/sex/group. The following neoplastic lesions were noted with a frequency exceeding 5% per group and sex: lungs (adenomas and carcinomas in males and females); liver (hepatocellular adenomas and hemangiosarcomas in males); testes (Leydig cell adenomas); seminal vesicles (granular cell tumors); ovaries (tubular adenomas, benign and malignant granulosa-theca cell tumors and luteomas); uterus (endometrial stromal polyp(s) and granular cell tumors); systemic neoplasias (malignant lymphomas in males and females and histiocytic sarcomas in males); Harderian glands (adenomas in males and females); mammary gland (adenocarcinomas in females).

It was reported that there were no apparent treatment-related neoplastic lesions. However, some findings (other than isolated incidences) of treated which exceeded that of controls (Groups 1, 2 controls thru high dose Gp 6) included: Male Livers - Hemangiosarcoma(M) 2, 2, 3, 1, 5, 3; Female liver - hemangiosarcoma 2 high dose only; Male Harderian glands - Adenoma(B) 2, 2, 1, 5, 5, 2; Female Harderian Glands - Adenocarcinoma(M) -, -, 1, 1, 1, 2; Female Skin/Subcutis - Malignant Schwannoma -, -, -, 2, 1, 1; Male Systemic Neoplasias - Mast Cell Tumor 1 in Gp 2 control and 2 in high dose.

NOTE: According to analysis by FDA (HFD-715) the positive linear dose-response trend for liver hemangiosarcoma in female mice indicated that this trend was statistically significant ($p=0.0248$). Additional trend analyses requested by this reviewer focusing on tumors, hemangioma and/or hemangiosarcoma across organs, showed no positive linear dose-response trend in the mice (male and female).